respectfully submit that the present application is in condition for immediate allowance based on the discussion which follows.

Claims 1-38 and 79-88 were rejected under 35 U.S.C. §§ 101 and 112 first paragraph and second paragraph. Further, claims 1-38 and 79-88 were rejected under 35 U.S.C. § 102(b) as being anticipated by, or in the alternative under 35 U.S.C. § 103(a) as being obvious over Yamada (CA 125:345266), Fenton (CA 125:10758), Psiorz (CA 116:41309), and Witek (CA 89:210420). Without addressing the merits of the rejections, Applicants have canceled claims 1-88 without prejudice and disclaimer and have added new claims 89-123 which are not disclosed or suggested in the prior art references.

New claims 89-123 are directed to the use of a ligand of histamine H_3-receptors having the formula $-NR^1R^2$ where R^1 and R^2 are suitably substituted as claimed. Novelty of the claimed invention, lies in part by the surprising discovery that an imidazole group which is present in known ligands of histamine H_3-receptors may be replaced by a suitable $-NR^1R^2$ group as claimed (see specification, pages 2-4). The inventors found that unexpectedly, (1) the claimed non-imidazoles analogs provide both an effective antagonist and/or agonist activity and (2) have a toxicity which is lower than the toxicity of corresponding imidazoles (specification, page 2, lines 15-27).

Moreover, even more surprisingly, the inventors further discovered that the transposition is possible in the general case. In other words, the inventors have discovered that if an imidazole group acts as a ligand of histamine H_3-receptors when substituted in the 4(5) position by a [W] group, e.g., [W]-imidazole, then a corresponding

[W]-NR^1R^2, non-imidazole analogue, provides an effective activity as agonist and/or antagonist of the histamine R_3-receptor with a lower toxicity than the [W]-imidazole.

Applicants respectfully submit that new claims 89-123 posses unity of invention in accordance with 37 C.F.R. § 1.475 as all claims are directed to a common, special technical feature. Specifically, claims 89-123 are directed to a method of using a suitably substituted N-R^1R^2 as a ligand of histamine H_3-receptors for various applications as claimed. In the generic case, the suitably substituted N-R^1R^2 has the formula (A) (e.g., new claim 123 which corresponds to original claim 1). In a more specific form, the suitably substituted N-R^1R^2 is in the form of formula (IIa) (e.g., claims 89-122). Therefore, Applicants respectfully submit that new claims 89-123 provide unity of invention.

Further, Applicants respectfully submit that new claims 89-123 are not anticipated and non-obvious over the cited art which was the subject of the Office Action. The Abstract of Yamada, Fenton and Witek disclose compounds of the formula (IIa) as summarized in the table below:

Citation	R^1	R^2	$(Ch.A^{II})$	X^{II}	$(CH.B^{II})$	Y^{II}
Yamada	Et	Et	CH_2	Net	CH_2	CH_3
Fenton	Et	Et	$(CH_2)_2$	Net	CH_2O	Et
Witek*	CH_3	CH_3	CH_2	0	CH_2	CH_3

* salt

Contrary to the disclosures of the aforementioned references, there fails to be any teaching or suggestion to use the disclosed compounds for use as a ligand of the histamine H_3-receptor. The compounds of Yamada and Fenton are merely described as "ligands" without specifying any affinity for the histamine H_3-receptor. Similarly, the salts of Witek are merely described as fungicides.

With respect to the disclosure of Psiorz, the Abstract of Psiorz fails to teach or suggest compounds whose structure matches the formula (IIa). Furthermore, the compounds of Psiorz fail to teach or suggest the specific and claimed (chain B^{II})-Y^{II} group. Moreover, Psiorz fails to teach or suggest the potential action of its compounds as a ligand of histamine H_3-receptor as no such use is contemplated. The disclosure of Psiorz merely discloses compounds which are described as cardiovascular agents. Therefore, Psiorz fails to teach or suggest the use of its compounds for treatment of the specific disorders/diseases as claimed in new claims 89-123.

In summary, as shown above, the individual and arguendo combined teaching of the aforementioned four references fail to teach or suggest the use of their respective compounds, some of which are of formula (IIa), would have a possible use as a histamine H_3-ligand. Furthermore, one of ordinary skill would not have found any incentive or motivation in the aforementioned references to make a compound of formula (IIa) for treating any of the afflictions of claims 89-123. Therefore Applicants respectfully submit that new claims 89-123 are not anticipated by or made obvious from the cited prior art.

With respect to the Examiner's rejection of claims 1-38 and 79-88 under 35 U.S.C. § 112, first paragraph, Applicants respectfully submit that new claims 89-123 contain subject matter described in the specification in a way to enable one of ordinary skill in the art to make and/use the invention. The Examiner had previously asserted that the now canceled claims were directed to compounds which had "massive differences in activities with little difference in structures" thereby not allowing an ordinary artisan to determine how to extrapolate to other compounds not specifically

made and tested. Specifically, the Examiner stated, "the specification and claims state that W is a residue which has activity when attached to imidazole. However, the moiety W is not attached to an imidazole ring in the present claims. So how can the compound have activity?"

New claims 89-123, which are directed to the use of compounds having the formula (IIa), are clearly described in the specification to enable one of ordinary skill to provide active compounds. None of the compounds disclosed provide particularly higher activity relative to any other compound. Furthermore, differences in activity shown in the examples cannot be regarded as "massive".

With respect to the previous objection concerning the definition of the W group, as noted above, the present invention is directed to the use of a suitable N-R^1R^2, substituted as claimed as a replacement for compounds having an imidazole group acting as a ligand of histamine H_3-receptors. For example, in new claim 123, "W" is defined as residue which imparts antagonistic and/or agnostic activity at histamine H3-receptor <u>if</u> W were to be attached to an imidazole ring in 4(5) position. W is defined in terms of known groups which act as ligands when attached to an imidazole ring. However, W of the claimed invention is <u>not</u> itself attached to an imidazole group.

The Examiner objected to the specification for including informalities on page 153 with respect to Examples 59 and 43. The Examiner stated that Example 59 has an ED_{50} = 0,20 and Example 43 has an ED_{50} = 0.50. By this Amendment, Applicants have submitted a replacement TABLE IV which changes the ED_{50} = 0,20 to ED_{50} = 0.20. Therefore, Applicants respectfully submit that the specification as amended obviates the rejection

Based on the foregoing discussions, Applicants respectfully submit that the present application is in condition for immediate allowance.

Respectfully submitted,

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